Diagnosing pulmonary embolism

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Objective testing for pulmonary embolism is necessary, because clinical assessment alone is unreliable and the consequences of misdiagnosis are serious. No single test has ideal properties (100% sensitivity and specificity, no risk, low cost). Pulmonary angiography is regarded as the final arbiter but is ill suited for diagnosing a disease present in only one-third of patients in whom it is suspected. Some tests are good for confirmation and some for exclusion of embolism; others are able to do both but are often non-diagnostic. For optimal efficiency, choice of the initial test should be guided by clinical assessment of the likelihood of embolism and by patient characteristics that may influence test accuracy. Standardised clinical estimates can be used to give a pre-test probability to assess, after appropriate objective testing, the post-test probability of embolism. Multidetector computed tomography can replace both scintigraphy and angiography for the exclusion and diagnosis of this disease and should now be considered the central imaging investigation in suspected pulmonary embolism.

Thrombotic pulmonary embolism is not an isolated disease of the chest but a complication of deep venous thrombosis (DVT). DVT and pulmonary embolism are therefore parts of the same process, venous thromboembolism (VTE). Evidence of leg DVT is found in about 70% of patients who have sustained a pulmonary embolism.1 Conversely, pulmonary embolism occurs in up to 50% of patients with proximal DVT of the legs (in the popliteal and/or more proximal veins), and is less likely when the thrombus is confined to the calf veins. Rarely, the source of emboli are the iliac veins, renal veins, right heart, or upper extremity veins; the clinical circumstances usually point to these unusual sites.7

The sequential course of most cases of VTE, with progression from calf DVT to proximal DVT and subsequently to pulmonary embolism, has important diagnostic implications. First, identifying asymptomatic DVT can, indirectly, establish the diagnosis of pulmonary embolism; this is helpful when initial tests for pulmonary embolism are non-diagnostic.1 4 Second, if proximal DVT can be excluded, there is a low short term risk of pulmonary embolism with non-diagnostic test for pulmonary embolism at presentation.5 7 Third, if proximal DVT is excluded at presentation and does not develop within two weeks, patients with non-diagnostic tests for pulmonary embolism have a low long term risk of subsequent VTE.5 7

RISK FACTORS AND RISK STRATIFICATION

The factors predisposing to VTE broadly fit Virchow’s triad of venous stasis, injury to the vein wall, and enhanced coagulability of the blood (box 1). The identification of risk factors aids clinical diagnosis of VTE and guides decisions about repeat testing in borderline cases. Primary “thrombophilic” abnormalities need to interact with acquired risk factors before thrombosis occurs; they are usually discovered after the thromboembolic event. Therefore, the risk of VTE is best assessed by recognising the presence of known “clinical” risk factors. However, investigations for thrombophilic disorders at follow up should be considered in those without another apparent explanation. In many patients, multiple risk factors are present, and the risks are cumulative.1 Half of the patients develop VTE while in hospital or in long term care, and the rest are equally divided between idiopathic cases and those with recognised risk factors.4 Many cases go unrecognised and hence untreated, with serious outcomes.

Although the overall frequency of pulmonary embolism cannot be accurately estimated, it is possible to assess incidence in particular groups at risk (table 1). In surgical series the risk of VTE rises rapidly with age, length of anaesthesia, and the presence of previous VTE or cancer. The incidence is highest in those undergoing emergency surgery following trauma (for example, for hip fractures) and pelvic surgery. In obstetrics there is a high incidence of VTE, particularly if operative delivery is used. Surgery predisposes patients to pulmonary embolism even as late as one month postoperatively. In medical patients, VTE is frequent in cardiorespiratory disorders (for example, congestive cardiac failure, severe chronic airways disease), with leg immobility (due to stroke and other neurological diseases) and in cancer.2

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

As both the extent and duration of embolic obstruction vary widely, pulmonary embolism can produce widely differing clinical pictures. Disregarding chronic thromboembolic pulmonary

Abbreviations: CTPA, computed tomography pulmonary angiography; DSA, digital subtraction angiography; DVT, deep venous thrombosis; MRI, magnetic resonance imaging; Pa(O2), arterial oxygen (carbon dioxide) pressure; PO2, oxygen pressure; VTE, venous thromboembolism
sometimes the first abnormality the patient notes results from pulmonary infarction, which occurs in obstruction of medium sized pulmonary artery branches. Sharp pleuritic pain develops, and there may be associated haemoptysis. The patient is breathing rapid and shallow because of the pleuritic pain, but is not cyanosed because the disturbance of gas exchange is only slight. Signs of pulmonary infarction may be found: a mixture of consolidation and effusion, possibly with a pleural rub. Fever is common and sometimes differentiates from infective pleurisy is difficult. The fever and pain often produce a sinus tachycardia. As minor pulmonary embolism does not compromise the right ventricle, cardiac output is well maintained, hypotension does not occur, and the venous pressure and heart sounds are normal. A common misapprehension is that there is often a loud pulmonary component of the second heart sound; this is not the case because the right heart pressures are normal or only slightly raised.

**Acute massive pulmonary embolism**

When >90% of the pulmonary circulation is suddenly obstructed, there is a substantial increase in right ventricular afterload and, if the cardiac output is to be maintained, consequent elevation of pulmonary artery systolic pressure and increase in right ventricular work. If this work cannot be sustained, acute right heart failure occurs. The right ventricular end diastolic pressure and right atrial pressure rise to about 15–20 mm Hg as the ventricle fails. Right ventricular dilatation leads to tricuspid regurgitation and may compromise the filling of the left ventricle. Cardiac output falls and the patient becomes hypotensive. The fall in aortic pressure and the rise in right ventricular pressure may cause ischaemia of the right ventricle through a critical reduction of right coronary perfusion.

Arterial hypoxaemia correlates roughly with the extent of embolism if there is no prior cardiopulmonary disease. Massive pulmonary embolism without hypoxaemia is so rare that if the arterial oxygen pressure (PaO₂) is normal an alternative diagnosis should be considered. The main causes of hypoxaemia are ventilation-perfusion mismatch, shunting through areas of collapse and infarction and/or through a patent foramen ovale, and low mixed venous oxygen saturation due to the reduced cardiac output. Hypoxaemia decreases tissue oxygen delivery and can impede circulatory adaptation through its vasodilating effects.

The clinical features of acute massive pulmonary embolism can be explained in terms of these pathophysiological changes (table 2). The patient becomes acutely distressed, severely short of breath, and may be syncopal due to the combination of hypoxaemia, and low cardiac output. The combination of hypoxaemia, hypotension, and increased cardiac work may cause anginal chest pain. The physical

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**Box 1: Risk factors for venous thromboembolic disease**

**Acquired factors—venous stasis or injury, secondary hypercoagulable states:**
- Immobilisation or other cause of venous stasis (for example, stroke, long travel).
- Major trauma or surgery within four weeks.
- Active malignancy (treatment within previous six months or palliative therapy).
- Previous proven venous thromboembolism.
- Reduced cardiac output (congestive heart failure).
- Obesity, advanced age.
- Pregnancy, early puerperium, oestrogen use.
- Indwelling catheters and electrodes in great veins and right heart.
- Acquired thrombotic disorders—for example, antiphospholipid antibodies, heparin-induced thrombocytopenia, thrombocytosis, post-splenectomy.

**Hereditary factors—primary hypercoagulable states (thrombophilia):**
- Deficiency of antithrombin, protein C or S.
- Resistance to activated protein C (factor V Leiden).
- Prothrombin gene mutation (G20210A polymorphism).
- Raised plasminogen-activator inhibitor, plasminogen disorders.
- Hyperhomocysteinaemia.
- High plasma concentration of factor VIII.

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**Table 1: Incidence of venous thromboembolism in various risk categories**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>Age &lt;40 years</td>
<td>Age &gt;40 years</td>
<td>Age &gt;60 years</td>
</tr>
<tr>
<td>Surgery &lt;30 min</td>
<td>No risk factors</td>
<td>No other risk factors</td>
<td>Hip or knee surgery, hip fracture, polytrauma</td>
</tr>
<tr>
<td>Orthopaedic surgery,</td>
<td>Minor trauma</td>
<td>Leg plaster cast</td>
<td></td>
</tr>
<tr>
<td>traumatology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical conditions</td>
<td>Pregnancy</td>
<td>Heart failure, stroke,</td>
<td>Long immobility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>malignancy</td>
<td></td>
</tr>
</tbody>
</table>

**Incidence, %**

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal DVT</td>
<td>0.2</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>0.4</td>
<td>0.8–2.0</td>
<td>0.8–2.0</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>0.2</td>
<td>0.2–0.4</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>0.002</td>
<td>0.01–0.02</td>
<td>0.01–0.02</td>
</tr>
</tbody>
</table>
signs are those of reduced cardiac output—that is, marked sinus tachycardia, hypotension, and a cool periphery. The patient is obviously dyspnoeic (but not orthopnoeic), cyanosed, and has signs of acute right heart strain: a raised venous pressure, which is often difficult to appreciate because of the respiratory distress, a gallop rhythm at lower sternal and a widely split second heart sound due to delayed right ventricular ejection, which is difficult to detect because of the accompanying tachycardia. The pulmonary component of the second heart sound is usually not loud because the pulmonary artery pressure is only moderately raised.

The reduction of left ventricular filling explains why the dyspnoea in patients with acute massive pulmonary embolism is eased by manoeuvres that increase systemic venous return and consequently left ventricular preload, such as lying flat or infusing colloid intravenously. This is in contrast to the dyspnoea of patients with left heart failure, which is eased by sitting upright and by interventions aimed at reducing left ventricular preload, such as diuretic treatment.

**Table 2 Clinical forms of pulmonary embolism**

<table>
<thead>
<tr>
<th>Pulmonary embolism</th>
<th>History</th>
<th>Vascular obstruction</th>
<th>Presentation</th>
<th>Typical pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute minor</td>
<td>Short, sudden onset</td>
<td>&lt;50%</td>
<td>Dyspnoea with or without pleuritic pain and haemoptysis</td>
<td>Normal</td>
</tr>
<tr>
<td>Acute massive</td>
<td>Short, sudden onset</td>
<td>&gt;50%</td>
<td>Right heart strain with or without haemodynamic instability and syncope</td>
<td>45/20</td>
</tr>
<tr>
<td>Subacute massive</td>
<td>Several weeks</td>
<td>&gt;50%</td>
<td>Dyspnoea with right heart strain</td>
<td>70/35</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure; RAP, mean right atrial pressure.

**Subacute massive pulmonary embolism**

This is caused by multiple small or moderately sized emboli that accumulate over several weeks. Because the obstruction occurs slowly, there is time for the right ventricle to adapt; consequently, the right ventricular systolic pressure is higher than in acute pulmonary embolism. The rises in the right ventricular end diastolic and right atrial pressures are of a lesser extent than in acute massive pulmonary embolism since there is time for adaptation to occur and the degree of right ventricular failure is less for a given degree of pulmonary artery obstruction. The main symptoms are increasing dyspnoea and falling exercise tolerance. The blood pressure and pulse rate are usually normal because the cardiac output is well maintained. Commonly, the venous pressure is raised and a third heart sound is audible at the lower sternal which may be accentuated by inspiration. There may also be intermittent symptoms and signs of pulmonary infarction that occurred during the build-up of the obstruction. In advanced cases, cardiac output falls and frank right heart failure develops. A further pulmonary embolus may change the picture to that resembling acute massive pulmonary embolism.

**DIAGNOSTIC PROCEDURES**

The diagnosis of pulmonary embolism is difficult, particularly when there is coexisting heart or lung disease and it is notoriously inaccurate when based on clinical signs alone. About two of three patients who present with suspected DVT or pulmonary embolism do not have these conditions. Very rarely, pulmonary embolism presents in such a dramatic fashion that the diagnosis is intuitively obvious and treatment will be started, but the usual presentation is frequently vague and variable in severity, so that further testing is necessary to establish or exclude the diagnosis.

**Estimating pre-test clinical likelihood of venous thromboembolism**

By adopting a thorough stratification system the clinician can make more appropriately select further investigations to prove or exclude pulmonary embolism, and predict the probability of pulmonary embolism after further objective testing (post-test probability). It helps to triage patients into clinically useful groups to avoid unnecessary testing, while minimising risk. For instance, when combined with a negative D-dimer test, the stratification excludes pulmonary embolism in outpatient with low pre-test probability. In patients with intermediate or high clinical probability, or inpatients, further testing is required.

Clinical likelihood of pulmonary embolism is determined after consideration of major risk factors (the commonest being immobilisation, lower limb fractures, and recent major surgery), presentation (including presence or absence of another reasonable clinical explanation), and basic investigations (electrocardiography and plain chest radiograph). The generally accepted characteristics of these clinical estimates are given in table 3.

Nearly all patients with pulmonary embolism will have one or more of dyspnoea of sudden onset, tachypnoea (>20 breaths/min), or chest pain (pleuritic or substernal)\(^a\); if the clinician remembers these three features, the possibility of pulmonary embolism will rarely be overlooked. When these clinical features are associated with electrocardiographic signs of right ventricular strain and/or radiological signs of plump hilum, pulmonary infarction or oligaemia, the likelihood of pulmonary embolism is high, and it is further strengthened in the presence of risk factors for VTE and arterial hypoxaemia with hypoacondia. On the contrary, the absence of all these three clinical features virtually excludes the diagnosis of pulmonary embolism.\(^a, b, c\) In the absence of major risk factors for VTE, paucity of typical signs for pulmonary embolism and/or DVT, and positive indications for the presence of an alternative diagnosis (for example, fever, radiographic evidence of pulmonary oedema or consolidation), the predicted likelihood of pulmonary embolism is low.

Several studies have shown that well characterised clinical empiric estimates or explicit prediction rules of pre-test likelihood of pulmonary embolism can be used for the safe management of patients suspected of having the disease.\(^a, 12-18\) However, these studies involved experienced clinicians using defined criteria under a research protocol; this is very different from the emergency room situation where decisions are often made by junior doctors whose ability to make an accurate estimate of the likelihood of pulmonary embolism is much less than that of their seniors. It is not clear if explicit
transoesophageal echocardiography, it is possible to visualise massive emboli in the central pulmonary arteries.21 In massive pulmonary embolism the right ventricle is dilated and hypokinetic, with abnormal motion of the interventricular septum. The inferior vena cava does not collapse during inspiration. Unfortunately, the finding of right ventricular dysfunction is non-specific20 and certain conditions commonly confused with pulmonary embolism (such as chronic obstructive pulmonary disease exacerbations or cardiomyopathy) are also associated with abnormal right ventricular function. The Doppler technique allows the detection of pulmonary hypertension, and together with contrast echocardiography it is useful in diagnosing patent foramen ovale which may indicate impending paradoxical embolism.

Although direct echocardiographic visualisation of intraluminal thrombi in patients with suspected pulmonary embolism is an almost exceptional event and even when echocardiography provides only indirect signs compatible with haemodynamic consequences of massive pulmonary embolism, it is helpful in excluding or suggesting alternative causes for haemodynamic instability (aortic dissection, ventricular septal rupture, cardiac tamponade, etc). In an unstable hypotensive patient requiring immediate treatment, such information is of great importance.22 However, because the right ventricle may show no dysfunction even in patients with massive pulmonary embolism, echocardiography should be considered an ancillary test rather than a principal diagnostic test for pulmonary embolism.20

### Arterial blood gases

The characteristic changes are a reduced \( P_{aO_2} \), and an arterial carbon dioxide pressure \( (P_{aCO_2}) \) that is normal or reduced because of hyperventilation. The \( P_{aO_2} \) is almost never normal in the patient with massive pulmonary embolism but can be normal in minor pulmonary embolism, mainly due to hyperventilation. In such cases the widening of the alveoloarterial oxygen gradient \( (>20 \text{ mm Hg}) \) may be more sensitive than \( P_{aO_2} \) alone. Both hypoxaemia and a wide alveoloarterial \( P_{aO_2} \) may obviously be due to many other causes. Blood gases, therefore, may heighten the suspicion of pulmonary embolism and contribute to the clinical assessment, but they are of insufficient discriminant value to permit proof or exclusion of pulmonary embolism.18 14 22

### Biochemistry

No blood test will diagnose pulmonary embolism. Although endogenous fibrinolysis is indicated by the sensitive assay of cross linked fibrin degradation products (D-dimers), this test has low specificity and is positive not only when there is VTE but also in the presence of disseminated intravascular coagulation, inflammatory disease, malignancy, and after trauma or surgery. Although a negative test may be strong enough evidence that clotting has not occurred and that anticoagulants can be withheld, a positive test cannot confirm VTE. The test can reduce the number of imaging investigations in outpatients with a low pre-test likelihood for VTE.20 26 27 However, if there is a high clinical suspicion of acute pulmonary embolism, diagnostic tests should proceed in spite of a normal D-dimer (in fact, D-dimer assay is useless in those with high clinical probability of pulmonary embolism). In elderly or inpatients, D-dimer retains a high negative predictive value, but is normal in less than 20% of patients, and, hence, not very useful.28

Not all D-dimer testing methods have sufficient sensitivity, but the rapid assays with a negative predictive value approaching 100% (for example, VIDAS DD) are comparable to the reliable but labour and time consuming conventional ELISA tests.17 25 Clinicians should know the characteristics of the test used in their hospital.
**Lung scintigraphy**

A normal perfusion scan essentially excludes the diagnosis of a recent pulmonary embolism because occlusive pulmonary embolism of all types produces a defect of perfusion. Normal results are almost never associated with recurrent pulmonary embolism, even if anticoagulants are withheld. However, a normal perfusion scan is found only in a minority (about a quarter) of patients suspected of having pulmonary embolism. The lung scan is an indirect method of diagnosis since it does not detect the embolus itself but only its consequence, the perfusion abnormality. Many conditions other than pulmonary embolism, such as tumours, consolidation, left heart failure, bullous lesions, lung fibrosis, and obstructive airways disease, can also produce perfusion defects. Addition of a ventilation scan increases the specificity of scintigraphy. Pulmonary embolism usually produces a defect of perfusion but not ventilation (‘mismatch’) while most of the other conditions produce a ventilation defect in the same area as the perfusion defect (matched defects). Pulmonary embolism can also produce matched defects when infarction has occurred, but in this situation the chest radiograph nearly always shows shadowing in the area of scan defect.

The probability that perfusion defects are due to pulmonary embolism can be assessed as high, intermediate, or low depending on the type of scan abnormality. If the scan is of a high probability type (multiple segmental or larger perfusion defects with normal ventilation) there is an >85% chance that the patient has pulmonary embolism. This implies that about 15% of patients with a high probability scan do not have pulmonary embolism and are therefore overtreated. The majority of patients with clinically suspected pulmonary embolism do not have high probability scans and instead have ones that suggest either low or intermediate probability (= non-diagnostic scans) and in these patients the prevalence of pulmonary embolism is about 25%. Taking the clinical assessment into account improves diagnostic accuracy (when the clinical likelihood of pulmonary embolism and scan interpretation is concordant, the ability to diagnose or exclude pulmonary embolism is optimised), but the diagnosis can still be made or excluded with accuracy in only about a third of patients. A low probability scan does not rule out pulmonary embolism, but in fact there is up to a 40% probability of pulmonary embolism when clinical likelihood is high. A ventilation scan is not indicated in cases with a subsegmental defect on the perfusion scan, because by definition this cannot lead to a high probability ventilation-perfusion scan. A ventilation scan is indicated in cases with segmental defects on the perfusion scan, otherwise it cannot lead to a high probability ventilation-perfusion scan. In theory the addition of ventilation scanning should improve the usefulness of perfusion imaging, but the PIOPED study showed such benefit to be marginal. Perfusion defects due to pulmonary embolism are most often wedge shaped. In the PIOSA-PED study, when only wedge shaped defects were classified as suspect for pulmonary embolism, perfusion scintigraphy without the use of ventilation scans, combined with clinical assessment of pulmonary embolism likelihood, enabled to confirm or exclude pulmonary embolism in 76% of patients with abnormal scans, with an accuracy of 97%. This suggests that where ventilation imaging is unavailable, perfusion scanning alone is acceptable. The simple PIOSA-PED criteria are an attractive alternative to the complex PIOPED criteria.

Although the lung scan is often an imprecise guide it is useful in clinical decision making: a normal scan or a low probability scan with low clinical likelihood of pulmonary embolism means that treatment for suspected pulmonary embolism can be withheld, and a high probability scan with a high clinical likelihood of pulmonary embolism means that treatment is mandatory. Further objective tests for DVT and/or pulmonary embolism must be used to decide on the therapy in patients between these extremes and in whom the clinical likelihood of pulmonary embolism and scan interpretation are discordant. An important principle is that in abnormal lung scans, the knowledge of clinical probability is essential in interpreting the report’s meaning but must not influence its description.

Planar scintigraphy is the standard technology in most institutions. With SPECT (single photon emission computed tomography) images can be reconstructed in any plane and the specificity of scintigraphy improves due to the reduction in the frequency of non-diagnostic scans. Scanning should be performed within 24 hours of the onset of symptoms suspect of pulmonary embolism, since some scans revert to normal quickly. A follow up scan at the time of termination of anticoagulant therapy is helpful in establishing a new baseline for subsequent episodes of suspected pulmonary embolism.

**Spiral computed tomography**

Spiral computed tomography with injection of contrast medium into an arm vein (computed tomography pulmonary angiography, CTPA) has emerged as a valuable method for diagnosing pulmonary embolism and because of its availability, it is becoming the first choice method at many institutions. The technique is faster, less complex, and less operator dependent than conventional pulmonary angiography, and has about the same frequency of technically insufficient examinations (about 5%). The thorax can be scanned during a single breath hold. There is better interobserver agreement in the interpretation of CTPA than for scintigraphy. Another advantage of CTPA over scintigraphy is that by imaging the lung parenchyma and great vessels, an alternative diagnosis (for example, pulmonary mass, pneumonia, emphysema, pleural effusion, mediastinal adenopathy) can be made if pulmonary embolism is absent. This advantage of CTPA also pertains to conventional pulmonary angiography, which images only the arteries. Computed tomography can also detect right ventricular dilatation, thus indicating severe, potentially fatal pulmonary embolism. Unlike lung scintigraphy, whose accuracy, assessed by comparison with pulmonary angiography, has large prospective trials will not change significantly in the future, both the accuracy and clinical utilisation of CTPA are likely to increase with technological advancements leading to improvement in data acquisition, particularly the use of thinner section collimation and multidetector computed tomography.

Criteria for a positive CTPA result include a partial filling defect (defined as intraluminal area of low attenuation surrounded by a contrast medium), a complete filling defect, and the “railway track sign” (masses seen floating in the lumen, allowing the flow of blood between the vessel wall and the embolus). CTPA also allows a quantitative assessment of pulmonary embolism severity which correlates well with clinical severity. The procedure has over 90% specificity and sensitivity in diagnosing pulmonary embolism in the main, lobar, and segmental pulmonary arteries. When CTPA is used to evaluate patients with a non-diagnostic lung scan, the sensitivity is lower. Although recent advances in computed tomography technology with 1–2 mm image reconstruction enable better visualisation of subsegmental arteries, these small vessels remain difficult to evaluate. The clinical significance of isolated subsegmental emboli (which account for about 20% of symptomatic pulmonary embolism) is unclear, and it is not
current practice to ignore them. They may be of importance in patients with poor cardiopulmonary reserve, and their presence is an indicator for current VTE, which thus potentially heralds more severe emboli. Recent studies showed, however, that patients with pulmonary embolism negative CTPA do well without anticoagulation therapy.\(^5\)\(^6\)\(^7\) This should be especially true when these patients also have a leg venous study that is negative for thrombus.\(^8\)\(^9\)\(^10\)

After performing CTPA to diagnose pulmonary embolism, sufficient opacification of the venous system remains to evaluate the veins of the legs, pelvis, and abdomen for DVT, without additional venepuncture or contrast medium. Such an examination adds approximately five minutes to pulmonary scanning, with the added expense of only one sheet of film. The pelvic and abdominal images screen the iliac veins and vena cava for thrombosis, an important advantage over sonography, particularly when caval filter placement is considered.\(^11\)\(^12\)\(^13\) If the accuracy of venous imaging after lung scanning is confirmed in large studies, its use should be considered whenever CTPA is indicated. Disadvantage is an increased radiation dose, particularly to the gonads.

**Magnetic resonance imaging (MRI)**

MRI offers both morphological and functional information on lung perfusion and right heart function, but its image quality still needs improvement to be comparable with computed tomography. Attractive advantage is the avoidance of nephrotoxic iodinated contrast and ionising radiation. This technique may ultimately allow simultaneous and accurate detection of both DVT and pulmonary embolism. A disadvantage of MRI compared with computed tomography is the long time needed to perform the examination, which is not suitable for clinically unstable patients. Improvements in MRI angiographic techniques will inevitably produce better results in the future\(^14\)\(^15\)\(^16\) but limited access is likely to continue for several years.

**Pulmonary angiography**

Catheter pulmonary angiography should be considered when other investigations are inconclusive.\(^17\)\(^18\) However, angiography has disadvantages of limited availability and a small (<0.3%) but definite risk of mortality.\(^19\)\(^20\)\(^21\) This risk gets higher the more seriously ill the patient is, particularly when there is significant pulmonary hypertension. Relative contraindications include pregnancy, significant bleeding risk, renal insufficiency, and known right heart thrombus. The safety of the procedure is enhanced by monitoring (electrocardiography, pulse oxymeter, automated blood pressure device), ready oxygen availability, and by reducing the amount of contrast material given at lower pressure.\(^2\)

Injection of low osmolar non-ionic contrast through a pigtail catheter into the main pulmonary artery is sufficient to delineate the emboli in most cases. Where prior scintigraphy is non-diagnostic, angiography can be first confined to the more abnormal side. When the embolus is small, selective injections into subdivisions of the arteries and oblique views improve diagnostic accuracy. The digital subtraction technique makes the examination easier and faster. An embolus appears as an abrupt vessel cut off or a convex filling defect often with contrast leaking beyond its edges and the sides of the vessel containing it. The overall perfusion of the affected region is reduced.

Conventional pulmonary angiography has been seen as the standard against which other imaging modalities have been historically evaluated. Of patients with normal pulmonary angiograms, about 1% have an episode of symptomatic VTE during the next six months\(^22\)\(^23\)\(^24\); this is the standard against which the safety of withholding anticoagulants after negative tests for pulmonary embolism is assessed. However, animal models that mimic subsegmental emboli have found sensitivity and positive predictive value of only 87%–88% compared with necropsy.\(^25\) Also, interobserver agreement of an angiographically documented subsegmental embolus is only about 70%.\(^26\) Consequently, pulmonary angiography remains the gold standard for central and segmental pulmonary embolism, but not for subsegmental pulmonary embolism. Comparable to asymptomatic calf vein thrombosis, an isolated subsegmental embolus may remain clinically asymptomatic without the need for anticoagulation. Prospective clinical outcome studies as to whether it will be safe to withhold anticoagulation in cases of isolated subsegmental embolism are lacking.

The changes in the right heart pressures that occur in pulmonary embolism are summarised in table 2. It is important to measure the pressures and oxygen saturations before angiography so that the haemodynamic situation, including cardiac output and any intracardiac shunting, can be assessed. This facilitates determination of the patient's underlying cardiopulmonary reserve, identification of any haemodynamic derangements that might require specific treatment to increase the safety of angiography, and more careful selection of the contrast agent and dose to maximise diagnostic information while minimising the risk. Occasionally if the suspicion of pulmonary embolism before catheterisation is wrong the haemodynamic data may suggest the correct diagnosis.

The use of intravenous digital subtraction angiography (DSA) avoids the need for pulmonary artery catheterisation but has been disappointing because opacification of the pulmonary vessels is poor. Although intravenous DSA may be adequate for showing large proximal arterial occlusions, resolution is inadequate to identify an embolus in the segmental vessels and beyond. Thus minor pulmonary embolism cannot be excluded on the basis of a normal DSA with peripheral contrast application.\(^27\)

**Search for (residual) deep venous thrombosis**

DVT cannot be reliably diagnosed on the basis of the history and physical examination. Patients with lower extremity DVT often do not exhibit pain, tenderness, redness, warmth, or swelling. When present, however, these findings merit further evaluation. Impedance plethysmography, compression ultrasonography, computed tomography venography and MRI are established non-invasive methods for diagnosing DVT. While contrast venography remains the gold standard, it is rarely performed because it is invasive and difficult to carry out in the acutely ill patient. Venography should only be performed whenever non-invasive testing is non-diagnostic or impossible to perform. While plethysmography and ultrasound are reliable for the diagnosis of symptomatic proximal DVT, they are much less reliable for recognising asymptomatic or distal DVT. They are also not able to detect floating thrombus in the vena cava. Plethysmography is inferior to the latest ultrasound techniques; it is now used in only a few institutions. The single well validated criterion for DVT on ultrasonography is the absence of full compressibility of the vein when applying pressure through the ultrasound probe. Doppler studies do not add significant diagnostic accuracy, as reduced flow is not specific for DVT and clots may be non-occlusive.\(^28\)

Computed tomography venography is very accurate, providing good visualisation of the proximal venous system and deep calf veins. As an added advantage, computed tomography venography can be combined with CTPA for a simultaneous investigation of both DVT and pulmonary embolism.\(^29\)\(^30\)\(^31\) Magnetic resonance venography, performed with time-of-flight and phase contrast imaging, is highly accurate at showing blood flow in the proximal venous system. Magnetic resonance direct thrombus imaging uses...
high signal generated from the thrombi to calculate the volume of intravenous clots and assess the risk of subsequent pulmonary embolism.\textsuperscript{37} Evaluation of pregnant women and patients with plaster casts is possible, as is differentiation between acute and chronic DVT and mimicking pathology. On the downside, the costs of MRI are high and the modality is not sufficiently available to be considered as a screening tool.

Although all the above methods for detecting thrombus in the deep veins do not establish the diagnosis of pulmonary embolism, the confirmation of DVT is of major importance in management decisions. The logic of leg vein imaging is that many patients with pulmonary embolism have residual proximal clot even in the absence of clinical evidence of DVT, itself an indication for treatment even if there is no direct proof of pulmonary embolism. If there is no thrombosis in the proximal leg or pelvic veins the chance of a further significant pulmonary embolism is low\textsuperscript{3-7} and therefore, even if a small pulmonary embolism has occurred already anticoagulation can be omitted. This approach needs caution if the patient has inadequate cardiorespiratory reserve, is likely to remain immobile, or if there could be an embolic source elsewhere (for example, right atrium or vena cava).\textsuperscript{3} Also, a negative single examination by ultrasound does not reliably exclude VTE, except in the few patients with no major risk factors and no clinical suspicion of DVT. A normal repeat ultrasonography, while it does not rule out distal thrombosis, identifies patients with a very low risk (<1%) of recurrent thromboembolism when left untreated. However, the diagnostic yield of serial ultrasound studies is very low, making this strategy unlikely to be cost effective.

Failure to identify thrombosis of the calf veins rarely has serious sequelae, and the investigation can be repeated if there is persisting clinical concern. In patients with documented isolated calf vein thrombosis, repeated compression ultrasonography can be used to separate the 20% of patients who develop proximal extension (and require treatment) from the remaining 80% of patients who do not and in whom the risks of anticoagulant therapy may outweigh the benefits (for example, in patients at high risk of bleeding).\textsuperscript{3-8}

INTEGRATED DIAGNOSTIC APPROACH WITH MANAGEMENT OPTIONS

The diagnosis requires a high level of clinical suspicion, estimation of the pre-test clinical likelihood of pulmonary embolism, and the judicious use of objective investigations to confirm or refute the suspicion. Pulmonary angiography is regarded as the final arbiter but is not often performed, due to its limited availability, costs, and invasiveness. Therefore, treatment is often based on clinical probability of pulmonary embolism rather than on a definite diagnosis or ruling out of the condition. Consequently, some patients receive anticoagulants without proof of pulmonary embolism and other patients are not treated, although they may have pulmonary embolism. For these reasons, much effort has been invested to determine how clinicians could reliably use non-invasive tests, alone or in combination, to replace pulmonary angiography as a diagnostic tool.

The approaches to the diagnosis of pulmonary embolism that minimise the use of pulmonary angiography are based on two guiding principles. In order for a test, or a combination of tests, to be considered accurate enough to diagnose the presence of pulmonary embolism, it should have a positive predictive value of more than 95%. To exclude a presence of pulmonary embolism, such a test should have a negative predictive value of more than 99%, as compared with pulmonary angiography, or be associated with less than 2% incidence of VTE during follow up if it is the base for withholding treatment. Near perfect sensitivity is important because, for every 2% decrease in sensitivity, one per 1000 patients studied will die of recurrent pulmonary embolism as a result of inappropriately withholding anticoagulation. The test results that effectively exclude or confirm pulmonary embolism are summarised in box 2.

Various combinations of tests have resulted in several elaborate algorithms\textsuperscript{7 11 12 17 24 26 27 31 32 56 76} which, however, are seldom followed in clinical routine. The goal of the first diagnostic strategies introduced was to confirm rather than exclude the presence of pulmonary embolism. The more recently evaluated diagnostic approaches have focused on identifying patients who probably do not have pulmonary embolism and therefore do not require anticoagulant therapy.\textsuperscript{74} Algorithms that inevitably result in large numbers of patients being referred for angiography are unhelpful. The availability of and familiarity with certain technology as well as the specific clinical scenario may influence the diagnostic approach. There is no single algorithm to be recommended for all situations; rather, the investigations should be chosen according to the haemodynamic state of the patient (suspicion of massive or minor pulmonary embolism), the onset of symptoms (in or out of hospital), the presence or absence of other cardiopulmonary diseases, and the availability of specific tests.

Basic tests

Basic tests include electrocardiography and plain chest radiography. These must be performed in all patients both to support clinical suspicion of pulmonary embolism and, in particular, to exclude alternative diagnoses. As electrocardiographic and chest radiographic abnormalities in pulmonary embolism may be non-specific, absent, transient, or delayed, they cannot be used to confirm the diagnosis. However, they are important in estimating the prior probability of the disease.\textsuperscript{5} Normal blood gases do not rule out pulmonary embolism; findings of hypoxaemia or hypopacipa may increase the physician’s level of suspicion, but they are not specific for pulmonary embolism. More specific investigations are always required, but choosing which road to follow from the many possibilities can be confusing.

<table>
<thead>
<tr>
<th>Box 2: Test results that effectively exclude or confirm pulmonary embolism</th>
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<tbody>
<tr>
<td><strong>Pulmonary embolism is excluded by:</strong></td>
</tr>
<tr>
<td>Normal pulmonary angiogram.</td>
</tr>
<tr>
<td>Normal perfusion scan.</td>
</tr>
<tr>
<td>Normal thin collimation (multidetector) CTPA.</td>
</tr>
<tr>
<td>Low probability perfusion scan and low clinical probability.</td>
</tr>
<tr>
<td>Normal D-dimer level (assay with high sensitivity) and low clinical probability.</td>
</tr>
<tr>
<td>Normal single detector spiral CTPA and compression ultrasonography (or computed tomography venography).</td>
</tr>
<tr>
<td>Non-diagnostic lung scan and normal results on serial leg testing.</td>
</tr>
</tbody>
</table>

| **Pulmonary embolism is confirmed by:** |
| Intraluminal filling defect on pulmonary angiogram. |
| Intraluminal filling defect on spiral CTPA. |
| High probability scan and moderate/high clinical probability. |
| Apparative evidence of acute DVT with non-diagnostic scan or spiral CTPA. |
Haemodynamic instability
In critically ill patients suspected of having massive pulmonary embolism, particularly those with cardiovascular collapse, transthoracic echocardiography should be rapidly performed at the bedside to exclude other diseases or, occasionally, to establish the diagnosis by finding clots in the central pulmonary arteries or the right heart. By visualisation of thrombi further investigations are not necessary. The finding of right ventricular dysfunction in a shocked patient with a normal left ventricular contractility would support (but not confirm) a diagnosis of pulmonary embolism, while its absence would make haemodynamically significant pulmonary embolism unlikely. When evidence of significant and otherwise unexplainable right heart strain without clots is present on transthoracic echocardiography, transoesophageal echocardiography should rapidly follow at the bedside. The finding of unequivocal thrombus in the pulmonary arteries by transoesophageal echocardiography has a very high specificity for pulmonary embolism, and warrants treatment without further testing if the diagnosis fits clinically. If transoesophageal echocardiography is unavailable, negative for pulmonary embolism or inconclusive, spiral CTPA or catheter pulmonary angiography should follow, depending on which is available with least delay. Should major pulmonary embolism be excluded, the correct diagnosis is usually evident with either procedure. Both procedures, however, may be constrained by logistic problems, including patient transportation. Catheterisation enables immediate rapid fragmentation of central emboli.

In patients with life threatening instability where emergency treatment is necessary and CTPA or cardiac catheterisation is unavailable, intravenous DSA may be adequate for showing large proximal arterial occlusions. Image quality can be improved by delivering the contrast to the pulmonary artery via a flow directed, balloon tipped catheter. The floating catheter is also useful in showing the characteristic haemodynamic changes with massive pulmonary embolism and suggesting an alternative diagnosis.

Haemodynamically stable patients
The principal challenge in stable patients is to develop a logical sequence of investigations that allow early, cost effective diagnosis and are associated with the most favourable markers of outcome. Depending on timely availability of tests, expertise required for their use, and on patient presentation, several approaches are possible.

(1) Proof of DVT without definitive diagnosis of pulmonary embolism
This should be the preferred first procedure in patients with clinical suspicion of DVT in addition to the suspicion of pulmonary embolism. If sonography, computed tomography, MRI, or impedance plethysmography confirms thrombosis, therapy can be started without recourse to lung imaging. Because the therapy of DVT and pulmonary embolism is the same in most patients with stable circulation, establishing the diagnosis of DVT is sufficient reason for full anticoagulation and avoids the need for additional studies. Leg vein imaging can also be performed as the initial investigation for suspected pulmonary embolism in patients with previous pulmonary embolism or chronic cardiopulmonary disease, where the frequency of non-diagnostic scans is high. If the leg study is negative or inconclusive, however, further investigations are imperative.

(2) D-dimer
In outpatients with a low clinical likelihood of pulmonary embolism, a normal level of D-dimer rules any significant thromboembolism out; further investigations are not necessary. The use of a D-dimer test in combination with clinical probability assessment is rapid, convenient for the patient, and cost effective. However, a raised D-dimer level is a frequent non-specific finding in elderly and hospitalised patients, in whom the clinical usefulness of this test is low.

(3) Lung scintigraphy
In about one third of cases, lung scan either rules out the diagnosis (normal perfusion or low probability scan with low clinical likelihood of pulmonary embolism) or suggests a high enough probability of pulmonary embolism that, in case of concurrent high clinical likelihood of pulmonary embolism, therapy can be undertaken on the basis of its results without further investigations. The frequency of such diagnostic scans is greater in outpatients with no prior cardiopulmonary disease who have a normal chest radiograph, and especially in these patients scintigraphy is the preferred initial examination. By limiting the patients who undergo scintigraphy to those without demonstrable lung disease at chest radiography, one can reduce the number of indeterminate studies and select a group of patients whose scintigrams are likely to show normal or high probability
results. However, the presence of cardiopulmonary disease or indeed any critical illness should not deter clinicians from requesting a lung scan, if it is readily available.

In patients with non-diagnostic scan, or whose clinical likelihood of pulmonary embolism does not correlate with the scan result, further investigation is necessary. Of these patients, about 25% will prove to have pulmonary embolism and require anticoagulants; the other will have another disease as the cause of lung scan defects. CTPA may be useful in these patients owing to its efficacy in imaging alternative pulmonary pathology. In outpatients with non-diagnostic scan, low clinical likelihood of pulmonary embolism and no prior cardiopulmonary disease, the finding of a normal D-dimer level (measured by a test with nearly 100% sensitivity) can be used to reliably exclude VTE.5

If clinical likelihood is intermediate and the scan non-diagnostic, long term anticoagulation can probably be withheld if repeated examination of leg veins over a week is normal and the patient has no underlying cardiopulmonary disease.24 If the leg veins are clear it is reasonable to assume that the patient is not in imminent danger of a fatal recurrence. Those with underlying cardiopulmonary disease, where only a medium sized embolus could be fatal, require a more aggressive diagnostic approach.3

(4) Spiral CTPA

Because the results of scintigraphy are inconclusive in most cases, CTPA should be the initial imaging modality of choice, especially in patients known to have a high rate of indeterminate scintigrams (for example, all inpatients, patients with radiographic abnormalities, and patients with chronic obstructive pulmonary disease). If CTPA is positive for pulmonary embolism, no further examination is necessary. Also, if it is negative down to the subsegmental arteries, it is not necessary to perform another investigation.22 However, if the CTPA findings are normal in the presence of a high clinical likelihood of pulmonary embolism, the patient may undergo leg imaging to detect the presence of a DVT. If this test is negative and the clinical likelihood of pulmonary embolism remains high, catheter angiography that focuses on the distal pulmonary vasculature should be performed.

(5) Pulmonary angiography

Depending on local capabilities, this may sometimes be the most readily available investigation (especially in centres specialised in catheter treatment of acute coronary syndromes). It pinpoints the diagnosis in cases of high clinical likelihood of pulmonary embolism despite non-diagnostic findings on lung and leg imaging. Occasionally, pulmonary angiography is used when the clinical likelihood is low despite the fact that other tests indicate pulmonary embolism. Angiography is also indicated if there are special reasons why the diagnosis must be confirmed beyond doubt (for example, when the risk from anticoagulation is higher than normal or when suspected recurrent emboli have led to frequent admissions to hospital often in the absence of any firm evidence of VTE). Angiography may also be the preferred option where serial testing is not feasible (for example, patient scheduled for surgery, geographic inaccessibility).

SUMMARY

No simple guidelines exist for the diagnosis of pulmonary embolism; rather, the investigations must be chosen according to the haemodynamic state of the patient, the onset of symptoms, the presence or absence of other cardiopulmonary diseases, and the availability of specific tests. With scintigraphy, pulmonary embolism can only be diagnosed or excluded in a minority of patients, and continuing attempts to refine technology and to redefine interpretative criteria will not materially improve this. On the contrary, the diagnosis of pulmonary embolism by computed tomography and MRI will continue to improve. To prevent haphazard and cost ineffective investigation of this commonly poorly managed condition, there should be at least one interested physician and radiologist who together review and refine both the hospital’s policy and its application in practice.

QUESTIONS (ANSWERS AFTER REFERENCES)

- Q1. Does a negative search for deep venous thrombosis reliably exclude the diagnosis of pulmonary embolism?
Q2. Pulmonary embolism is highly unlikely in the absence of all three of dyspnoea, tachypnoea, and chest pain (true/false).

Q3. Hypotension without a high jugular venous pressure is not caused by pulmonary embolism (true/false).

Q4. Is hypoxaemia with hypocapnia pathognomonic for pulmonary embolism?

Q5. Proof of proximal DVT avoids the need for definitive diagnosis of pulmonary embolism (true/false).

Q6. Does low probability scan reliably exclude pulmonary embolism?

Q7. Perfusion imaging alone, without ventilation scan, is useless (true/false).

Q8. In patients with chronic cardiopulmonary disease, scintigraphy is preferable to computed tomography (true/false).

Q9. Echocardiography should be performed immediately in suspected massive pulmonary embolism with haemodynamic instability (true/false).

Q10. Spiral CTPA can always prove or exclude massive central pulmonary embolism (true/false).

Q11. A raised level of plasma D-dimer is sufficiently specific to be diagnostic of DVT or pulmonary embolism (true/false).

REFERENCES


Diagnosing pulmonary embolism


ANSWERS